pseudomonas, borrelii, citrobacter, escherichia, salmonella, propionibacterium, treponema, shigella, enterococci, and leptospirex; and

(b) a pharmaceutically acceptable carrier.

REMARKS

After amending the claims as set forth above, claims 23-33, 35-47, 49, and 50 are now pending in this application. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

I. Summary of the Amendments to the Specification and Claims

The application has been amended to recite the depository numbers for the virulent bacteriophage 146A and 173A preparations. In addition, claims 23 and 37 have been amended to clarify that the claims recite bacteriophage strains.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is courteously requested.

II. Summary of the Claimed Invention

The claimed invention is directed to methods of treating mammals suffering from a bacterial infection with a purified, virulent, non-toxic, host-specific bacteriophage preparations having a wide host range. *See e.g.*, page 1, lines 4-6; and page 4, lines 14-16, of the application. The characteristics of the claimed bacteriophage preparations result from the selection method employed. The selection method acts as a screening mechanism to identify the claimed novel bacteriophage preparations.

The present invention overcomes the problems encountered in the prior art and provides simple, efficient, and superior methods for using bacteriophage preparations.

III. **Rejections under 35 U.S.C. § 112**

Claims 23, 24, 37, and 47-48 were rejected under 35 U.S.C. 112, second paragraph, for alleged indefiniteness. In support of this ground for rejection, the examiner alleged that claims 23 and 37 were unclear with regard to the number of bacteriophages administered. Specifically, the examiner found it unclear whether there were 2 or more bacteriophage strains or organisms. Applicants respectfully traverse this ground for rejection.

The specification teaches that the claimed invention encompasses bacteriophage *strains*, and not *organisms*. Accordingly, claims 23 and 37 have been amended to make it explicit rather than implicit that there are two or more bacteriophage strains administered, each bacteriophage strain being selected against one of the enumerated bacterial genera. Claim 23 has also been amended to clarify that two or more bacteriophage strains are also isolated from different bacterial strains. Applicants note that the claims have not been narrowed by the addition of the term "strain," but rather the claim amendments only make explicit what was implied, which is evident from the specification. Because Applicants' claims are definite, withdrawal of this ground for rejection is respectfully requested.

The examiner also found the term "substantially kill" unclear. While Applicants respectfully disagree with the Examiner's rejection, this phrase has been deleted for the sole purpose of advancing the prosecution of this case.

Continuing, with regard to claims 33 and 47, the examiner found it unclear how the preparation could be resistant to the different enumerated conditions. The claims must be interpreted in light of the specification, of which they are a part, from the standpoint of one of ordinary skill in the art. The specification explains how to select for bacteriophages that have resistance to the enumerated environmental conditions. *See e.g.*, page 5, lines 24-30; page 7, lines 4-10; page 11, lines 19-22; page 14, lines 7-24; and page 21, lines 6-12. Thus, Applicants respectfully submit that claims 22 and 47 are not clear when read in light of the specification by one of ordinary skill in the art. Accordingly, Applicants' claims are definite.

Finally with regard to claims 34 and 48, the examiner found the terms "normal or abnormal conditions" unclear. While Applicants respectfully disagree with this ground for rejection, these claims have been cancelled for the sole purpose of advancing the prosecution of this case.

IV. Rejections under 35 U.S.C. § 102

A. Merril et al., U.S. Patent No. 5,688,501

Claims 23-25, 29-30, 33-39, 43-44, and 47-50 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Merril et al., U.S. Patent No. 5,688,501. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

In support of this ground for rejection the Examiner alleged that Merril et al. teach the administration of an effective amount of bacteriophage for a time to substantially kill the bacterial organisms in a mammal, including bacteriophages specific to the same bacterial genera claimed in the present invention, and lyophilized preparations, ionic variation resistance, additional antibiotics.

2. Merrill et al. Do not Teach Virulent Bacteriophage Having a Broad Host Range

Merrill et al. is directed to bacteriophage, developed by either serial passage (mutagenized or non-mutagenized) or genetic engineering, that are capable of delaying inactivation by any component of an animal's host defense system (HDS) against foreign bodies. *See* col. 3, lines 52-56, of Merrill et al. Serial passage is accomplished by administering the phage to an animal and obtaining serial blood samples over an extended period of time. Eventually, a viable phage capable of delaying inactivation by the HDS is obtained. *See* col. 4, lines 50-56; and col. 5, lines 32-47, of Merrill et al. A sample of the remaining phage is then injected into a second animal of the same species, and the process is repeated, until a phage is obtained that can survive at least 15% longer in the body than the longest surviving wild-type phage. *See* col. 4, line 56, through col. 5, line 4, of Merrill et al. Alternatively, a phage can be genetically engineered such that it expresses molecules on its surface coat that antagonize,

inactivate, or in some other manner impede those actions of the HDS that would otherwise reduce the viability of the administered phages. *See* col. 5, lines 50-55, of Merrill et al.

This does not teach Applicants' claimed invention, directed to a purified, host-specific, non-toxic, wide host range and virulent bacteriophage preparation. In particular, Merrill et al. teach that the bacteriophage "are specific for each of the bacterial strains of interest." *See* col. 6, lines 63-67, of Merrill et al. Using this method, "a full array of anti-HDS selected and/or anti-HDS engineered bacteriophage is developed for virtually all the bacterial (and other applicable) pathogens . . . [to enable phage therapy]." *See* col. 6, line 67, through col. 7, line 5, of Merrill et al.

In contrast, the present invention is directed to bacteriophage which have a broad host range, rather than bacteriophage that are directed against a single strain. Merrill et al. require "a full array" of bacteriophage for treatment, while Applicants' claimed bacteriophage enable treatment with a single bacteriophage preparation. Accordingly, because the claimed invention is not anticipated by Merrill et al., withdrawal of this ground for rejection is courteously requested.

Thus, the examiner has failed to make out a prima facie case of anticipation because the examiner has not shown that Merril et al. discloses each and every one of the limitations of the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

B. Norris, U.S. Patent No. 4,957,686

Claims 23, 24, 33, 34, 37, 38, 47, and 48 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Norris, U.S. Patent No. 4,957,686. Applicants respectfully traverse this ground for rejection.

1. Examiner's Basis for Rejection

In support of this ground for rejection, the Examiner stated that Norris discloses the administration of a mixture of bacteriophages specific for different Streptococcus strains, with a pharmaceutically acceptable carrier.

2. Norris Does not Teach Virulent Bacteriophage Having a Broad Host Range

Norris is directed to bacteriophage against *Streptococcus sanguis*, which is the first colonizer of newly cleaned teeth. Other bacteria then attach to *S. sanguis*, leading to the formation of dental plaque. *See* col. 1, lines 63-68, of Norris. This does not teach Applicant's claimed invention, directed to host-specific, non-toxic, and virulent bacteriophage having a broad host range. Thus, the examiner has not shown that Norris discloses each and every one of the limitations of the claimed invention. Because the claimed invention is not anticipated by Norris, withdrawal of this ground for rejection is courteously requested.

C. Soothill, *J. Med. Microbiol.*, *37:*258 (1992)

Claims 23, 24, 33, 34, 37, 38, 47, and 48 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Soothill, J. *Med. Microbiol.*, *37:*258 (1992), which is alleged to disclose the administration of bacteriophages specific for *Pseudomonas aeruginosa* or *Staphylococcus aureus*, with a pharmaceutically acceptable carrier to a mammal. Applicants respectfully traverse this ground for rejection.

The examiner has not shown that Soothill discloses each and every one of the limitations of the claimed invention. Specifically, Soothill does not teach administering two bacteriophage strains, a bacteriophage strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, as required by Applicants' claims. Because Applicants' claimed invention is not anticipated by Soothill, withdrawal of this ground for rejection is respectfully requested.

D. Sakandelidze, 1991 (Abstract)

Claims 23, 35, 37, and 49 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Sakandelidze, 1991 (Abstract), which is alleged to disclose the administration of a bacteriophage specific for a bacterial host, with an antibiotic, in a pharmaceutically acceptable carrier. Applicants respectfully traverse this ground for rejection.

The examiner has not shown that the Sakandelidze abstract discloses each and every one of the limitations of the claimed invention. Specifically, the Sakandelidze abstract does not teach administering two bacteriophage strains, a bacteriophage strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, as required by Applicants' claims. The Sakandelidze abstract also says nothing about the toxicity or purity of the formulation administered. Because Applicants' claimed invention is not anticipated by this reference, withdrawal of this ground for rejection is respectfully requested.

E. Bogovazova, 1991 (Abstract)

Claims 23, 24, 37, and 38 were rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Bogovazova, 1991 (Abstract), which is alleged to disclose the administration of a bacteriophage specific for *Klebsiella pneumoniae*, in a pharmaceutically acceptable carrier. Applicants respectfully traverse this ground for rejection.

The examiner has not shown that the Bogovazova abstract discloses each and every one of the limitations of the claimed invention. Specifically, the Bogovazova abstract does not teach administering two bacteriophage strains, a bacteriophage strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, as required by Applicants' claims. The Bogovazova abstract also says nothing about the toxicity or purity of the formulation administered. Because Applicants' claimed invention is not anticipated by this reference, withdrawal of this ground for rejection is respectfully requested.

V. Rejections under 35 U.S.C. § 103

A. Merril et al., U.S. Patent No. 5,688,501, and Denney, U.S. Patent No. 3,793,151

Claims 26 and 40 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, which is alleged to disclose the administration of a bacteriophage specific to Streptococcus in a pharmaceutically acceptable carrier, in view of Denney, U.S. Patent No. 3,793,151, which is alleged to

disclose a phage specific to *S. pyrogenes*. Applicants respectfully traverse this ground for rejection.

The examiner has failed to make out a prima facie case of obviousness. As discussed above, Merril et al. do not teach administering two or more bacteriophage strains, as required by the claims. Merril et al. also do not disclose a preparation containing a bacteriophage strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, which is also required by the claims.

Denny does not remedy the deficiencies of Merill et al., as this reference also does not teach administering two or more bacteriophage strains, a bacteria strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates. Thus, given the disclosures of Merril et al. and Denny, one of ordinary skill in the art at the time the claimed invention was made could not have obtained the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

B. Merril et al., U.S. Patent No. 5,688,501, and He et al, 1992 (Abstract)

Claims 27 and 41 were rejected under 35 U.S.C. § 103 as being allegedly obvious over Merril et al., U.S. Patent No. 5,688,501, which is alleged to disclose the administration of a bacteriophage specific to Streptococcus in a pharmaceutically acceptable carrier, in view of He et al., 30 J. Clin. Microbiol. 590 (1992) (Abstract), which is alleged to disclose a phage specific to *Citrobacter freundii*. Applicants respectfully traverse this ground for rejection.

The examiner has failed to make out a prima facie case of obviousness. As discussed above, Merril et al. do not teach administering two or more bacteriophage strains, as required by the claims. Merril et al. also do not disclose a preparation containing a bacteriophage strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, which is also required by the claims.

He et al. does not remedy the deficiencies of Merill et al., as this reference also does not teach administering two or more bacteriophage strains, a bacteria strain that has a wide host range, or a bacteriophage strain that is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates. Thus, given the disclosures of Merril et al. and Denny, one of ordinary skill in the art at the time the claimed invention was made could not have obtained the claimed invention. Withdrawal of this ground for rejection is respectfully requested.

VI. Conclusion

In light of the foregoing amendments and arguments, Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date February 19, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please replace the last paragraph on page 24 of the specification and the first paragraph on page 35 of the specification with the following new paragraphs:

Two particularly virulent preparations were selected on the basis of concentration and isolate sensitivity. CsCl purified preparations 146A and 173A were capable of killing the majority of different isolates, and were virulent at a concentration of 100 times less than the least virulent preparation. Purified 146A and 173A phage preparations were tested against 52 different *E. coli* isolates, whereby 146A plaqued against 22 isolates (42%) and 173A plaqued against 20 isolates (38%). Combined, these two phage preparations were effective against 31 of the 52 isolates (60%). In comparison, a purified 222A phage preparation was found to be effective in killing only 6 isolates (11.5%). Purified 146A and 173A *E. coli* bacteriophage preparations were then characterized by: (i) plaque morphology (the 146A preparations provided clear plaques of 1-2 mm with defined edges, and the 173A preparations provided plaques of 4-6 mm with clear centers of 2-3 mm and turbid haloes); (ii) electron microscopy (FIGS. 1 and 2); and (iii) DNA fingerprinting analysis (FIGS. 3 and 4). Samples of virulent bacteriophage 146A and 173A preparations were deposited in the ATCC, 12301 Parklawn Drive, Rockville, MD, 20852, on April 15, 1997 and accorded ATCC accession Nos. [___ and ___] 55950 and 55951, respectively.

Example 7

Bacterial cultures of *Citrobacter fruendii* and from *Klebsiella oxytoca* were obtained from urinary samples and purified. Host-specific plaque purified nontoxic bacteriophage preparations were selected, isolated, and purified from sewage filtrate using the procedures outlined above in Example 6, except that purified urinary cultures of *Citrobacter fruendii* and *Klebsiella oxytoca* were used. Virulent bacteriophage 262A preparations against *C. fruendii* were characterized by: (i) plaque morphology (the *C. fruendii* plaques had diameters of 2-4 mm with irregular edges and distinct centers; (ii) electron microscopy (FIG. 5); and (iii) DNA fingerprinting analysis. A samples of virulent bacteriophage 262A preparation was deposited in the ATCC at the above address, on April 15, 1997 and accorded ATCC accession No. [___] 55955. Virulent

bacteriophage 174 preparations against *K. oxytoca* were characterized similarly by plaque morphology, electron microscopy and DNA fingerprint analysis (FIG. 6). A sample of virulent bacteriophage 174A preparation was deposited in the ATCC at the above address on April 15, 1997 and accorded ATCC accession No. [___] 55956.

Please replace claims 23 and 37 with the following, amended versions of the same claims.

23. (Amended) A method of treating a mammal suffering from bacterial infection [by a bacterial organism,] comprising administering to the mammal an effective amount of a [bacteriophage] composition [for a period of time sufficient to substantially kill the bacterial organism, wherein the composition comprises] comprising:

(a) a purified, host-specific, non-toxic, wide host-range, and virulent bacteriophage preparation, wherein:

[(1) the bacteriophage preparation can be safely administered to patients or mammals in need:]

(1[2]) the bacteriophage preparation consists essentially of two or more bacteriophage strains, wherein each bacteriophage strain is selected against one of the group consisting of staphylococci, hemophilii, helicobacter, mycobacterium, mycoplasmi, streptococci, neisserii, klebsiella, enterobacter, proteus, bacteriodes, pseudomonas, borrelii, citrobacter, escherichia, salmonella, propionibacterium, treponema, shigella, enterococci, and leptospirex;

(2[3]) at least two of the bacteriophage strains are isolated against different strains of bacterial organisms; and

(3[4]) each bacteriophage strain is effective in killing, *in vitro*, bacteria from at least about 50% of bacterial isolates, wherein the isolates are from the same strain of bacterial organism as that from which the bacteriophage strain is isolated; and

(4) the bacteriophage preparation can be safely administered to patients or mammals in need; and

(b) a pharmaceutically acceptable carrier.

37. (Amended) A method of treating a mammal suffering from bacterial infection [by a bacterial organism], comprising administering to the mammal an effective amount of a [bacteriophage] composition [for a period of time sufficient to substantially kill the bacterial organism, wherein the bacteriophage preparation comprises] comprising:

(a) a purified, host-specific, non-toxic, wide host-range, and virulent bacteriophage preparation, wherein [(1)] the bacteriophage preparation consists essentially of two or more bacteriophage strains, [and] [(2)] wherein each bacteriophage strain is selected against one of the group consisting of staphylococci, hemophilii, helicobacter, mycobacterium, mycoplasmi, streptococci, neisserii, klebsiella, enterobacter, proteus, bacteriodes, pseudomonas, borrelii, citrobacter, escherichia, salmonella, propionibacterium, treponema, shigella, enterococci, and leptospirex; and

(b) a pharmaceutically acceptable carrier.